UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,968	07/31/2003	John J. Rossi	1954-401	3645

6449 7590 03/15/2011

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/15/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/630,968	ROSSI ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9,17,19-21 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9,17,19-21 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on January 28, 2011.

Currently, claims 3-9, 17, 19-21, and 33-38 are pending and under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Objections/Rejections Necessitated by Amendment

Claim Objections

Claims 17, 19-21, and 36-38 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In the instant case, claims 17, 19-21, and 36-38 depend from claim 33. Claim 33 is directed to "**An**" amplification-based method for producing "**a**" mammalian promoter-containing siRNA expression cassette. As such, claim 33 requires a single PCR that produces a single cassette.

Now, claims 17, 19-21, and 36-38 depend from claim 33, but require "two polymerase chain reaction amplifications are performed", thereby producing not a single cassette, but two cassettes: "a first amplified product" and "a second amplified product". Hence, claims 17, 19-21, and 36-38 have additional method steps with additional resultant products than the method steps/product of claim 33, thereby failing to further limit the method steps and a single product claimed in claim 33.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 3-9, 17, 19-21, and 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-9, 17, 19-21, and 34-38 depend from claim 33, which is newly added. Claim 33 recites "producing a mammalian promoter-containing siRNA expression cassette" in lines 1-2. With regard to the term "siRNA", the instant specification teaches that it refers to double-stranded RNAs of "21 to 23 nucleotide (nt) fragments". See paragraph 0004. Further, claim 33 itself refers to and further defines the term "siRNA" as being "double stranded". See step (iii). Hence, the instant claims are drawn to a method that produces double-stranded, short RNA fragments. As such, the claims require a method step that allows one to synthesize a double-

stranded, target-specific RNA, which is expressed as a double-stranded, target-specific siRNA when transfected into a mammalian cell. In the instant case, however, there is not a single method step that allows one to synthesize both strands (sense strand and antisense strand) of an siRNA sequence. Note that method step (iii) of claim 33 comprises a "second oligonucleotide primer" that hybridizes to **a** nucleotide sequence encoding "either a sense sequence of a double stranded siRNA molecule or an antisense sequence of the double stranded siRNA molecule". As such, performing the method steps recited in claim 33 would not result in an siRNA expression cassette that produces a double-stranded RNA molecule, wherein the term "siRNA" inherently and necessarily indicates a double-stranded RNA molecule. Hence, the claims have omitted method steps, wherein such omitted steps result in a gap between the intended product (a cassette that produces a double-stranded siRNA) and the resultant product (a cassette that produces only either one of the both strands). Hence, the claims are internally inconsistent, thereby rendering the claims indefinite.

With regard to claims 17, 19-21, and 36-38, which further recite a "second amplified product", it is found that the method steps/elements recited in claim 36 cannot depend properly from claim 33 because claim 33 is intended to produce only a single cassette with a single-stranded ("either a sense sequence of a double stranded siRNA molecule or an antisense sequence of the double stranded siRNA molecule") by performing "a" single PCR, whereas claim 36 requires two PCR methods, which independently produce a cassette having a sense strand of the double-stranded siRNA and a cassette having an antisense strand of the double-stranded siRNA. Hence, the methods of claims 17, 19-21, and 36-38 are internally inconsistent and conflict with the method of claim 33.

In addition, as mentioned hereinabove, claim 33 and thus its dependent claims must produce "a" single cassette encoding a double-stranded siRNA molecule. Again, note that the term "siRNA" inherently and necessarily indicates that it is a double-stranded molecule. Note also that the preamble of claim 33 explicitly points out that the claims in the instant application are to produce an "siRNA expression cassette", wherein again, the term "siRNA" refers to a short RNA molecule that is double-stranded. Now, as noted hereinabove, claims 17, 19-21, and 36-38 produce two independent cassettes ("a first amplified product" and "a second amplified product"), each of which encodes only one of the two strands of a double-stranded siRNA molecule. As such, the methods of claims 17, 19-21, and 36-38 fail to produce a single siRNA expression cassette that encodes a double-stranded siRNA molecule as intended by claim 33, as evidenced by the preamble language, an "siRNA expression cassette" and by virtue of the definition of the term "siRNA" that must be double-stranded.

In essence, when the actual method steps recited in the instant application are taken into consideration, it appears that applicant should be claiming a method that produces only one of the two strands (either sense strand or antisense strand) of a double-stranded siRNA molecule. Again, note that the preamble language ("siRNA expression cassette"; note the definition of the term "siRNA"; note that the cassette is a singular term, thus the claims must produce a single cassette that encodes a double-stranded siRNA) conflicts with the actual method steps that result in a cassette that encodes only one strand, single-stranded RNA. Further, as evidenced by claims 17, 19-21, and 36-38, one must perform two separate, independent methods so as to produce two separate, independent cassettes, each encoding only one of the two strands of a double-stranded siRNA molecule, followed by a method step of transfecting the two cassettes into a mammalian

cell. Only then, can one actually produce a truly double-stranded RNA molecule in a mammalian cell when the two separate, independent cassettes are transfected into the cell.

In view of the foregoing, it is concluded that the instant application does not contain "claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." as required by the second paragraph of 35 U.S.C. 112.

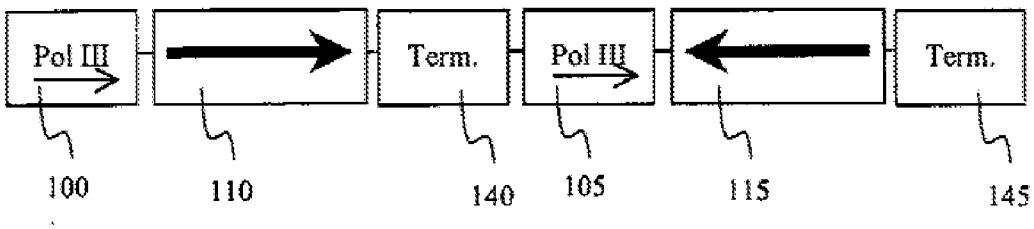
Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 3-9, 17, 19-21, and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lois-Caballe et al. (US 2003/0059944 A1) in view of MacFerrin et al., Lindermann et al., and Livache et al. (all citations of record).

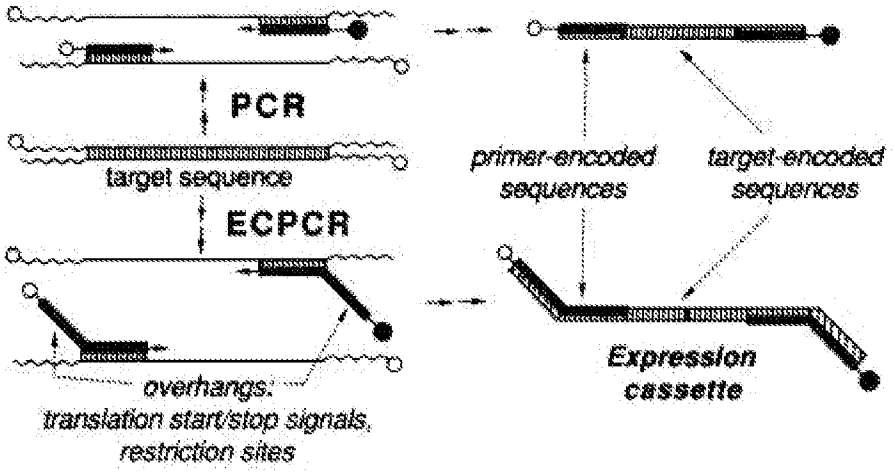
Lois-Caballe et al. teach that one can make an siRNA expression cassette comprising a pol III promoter (e.g., U6 promoter) operably linked to the sense strand of a double-stranded siRNA followed by a termination signal sequence and a pol III promoter operably linked to the antisense strand of the double-stranded siRNA followed by a termination signal sequence. See for example, Figure 3 as below:

FIGURE 3



They show that target gene expression is reduced when the siRNA expression cassette construct is transfected into cells. See paragraphs 0018, 0145-0146; claims 1, 11-12. They teach that one can make the siRNA expression cassette/construct by using "any suitable genetic engineering techniques well known in the art, including, without limitation, the standard techniques of PCR, oligonucleotide synthesis, restriction endonuclease digestion, ligation, transformation, plasmid purification, and DNA sequencing" (emphasis added). See paragraph 0073. Lois-Caballe et al. do not explicitly teach that the siRNA expression cassette is produced by a PCR-based amplification method.

MacFerrin et al. teach a PCR amplification-based method for producing a promoter-containing, double-stranded oligonucleotide expression cassette, termed "expression-cassette polymerase chain reaction (ECPCR)" as depicted in Figure 1 shown below:



MacFerrin et al. teach that ECPCR comprises a pair of primer oligonucleotides, one hybridizing to and encoding the expression cassette nucleotide sequence in the 3' region (e.g., transcription termination signal sequence) and the other hybridizing to and encoding the expression cassette nucleotide sequence in the 5' region (e.g., transcription start sequence;

promoter sequence). They teach that the primer oligonucleotides in the ECPCR protocol also contain restriction enzyme site sequences to introduce restriction enzyme sites into the expression cassette, thereby producing an expression cassette that is "suitably equipped for cloning." See page 1937. They teach that the "use of PCR to add new sequence information concomitant with amplification has found wide applicability in recombinant DNA technology, and the ECPCR protocol is representative of such methods. Particularly intriguing is the demonstration that the T7 promoter sequence can be added to target DNA in order to facilitate sequence analysis; indeed, those results indicate that it should be possible to engineer T7-based overproduction systems using an ECPCR-like strategy in combination with previously described vectors…The length of noncomplementary sequences added during ECPCR is primarily limited not by PCR amplification, but by the size limitation of automated DNA synthesis (routinely >100 nucleotides); hence, the potential exists to incorporate additional sequence motifs (e.g., synthetic promoters or periplasmic signal sequences) during the ECPCR procedure." See page 1940, right column.

Lindermann et al. teach that it is within the skill of the art to prepare primers capable of annealing to primer binding sites. They teach that one can make and use phosphorylated primer oligonucleotides. They teach that 5' end modifications on the primer oligonucleotides render the primer oligonucleotides resistant to a 5'-specific exonuclease. See column 18.

Livache et al. teach that the principle of PCR is "well known" (see column 5) and that one can use PCR to produce double-stranded nucleic acid, for example, a double-stranded promoter sequence (see column 2: "Promoter is understood to mean any double-stranded sequence of DNA comprising a binding site recognized by a DNA-dependent RNA polymerase")

such that "a template DNA proved with promoters can be specifically produced, from a nucleic acid sample, by a technique such as PCR, using primers containing promoter sequences for the amplification of the target sequence." See column 6, lines 12-15.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the expression cassette comprising the U6 promoter-siRNA sequence-termination signal sequence of Lois-Caballe et al. by utilizing the ECPCR protocol of MacFerrin et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to produce an siRNA sequence expression construct in a more facile manner, because the ECPCR procedure of MacFerrin et al. was suggested to be based on a PCR primer-based amplification method that allows incorporation of additional nucleotide sequences into an expression cassette during PCR amplification, thereby enabling a production of a desired expression cassette comprising a desired promoter sequence, a desired nucleotide insert sequence, a desired stop sequence, and desired restriction enzyme site sequences without the need to perform the laborious cloning and subcloning/ligation procedures. Note that MacFerrin et al. taught that ECPCR "facilitates overproducer construction by effecting site-specific replacement of the 5' and 3' ends of the gene with expression sequences derived from synthetic oligonucleotides." and that "ECPCR also takes advantage of the now-routine ability to introduce restriction sites via the polymerase chain reaction, yielding gene expression cassettes that are suitably equipped for cloning." See page 1937. As such, given the advantages associated with the alternative methodology (ECPCR) for producing an expression cassette and further given the fact that "use of PCR to add new sequence information concomitant with amplification has found

wide applicability in recombinant DNA technology, and the ECPCR protocol is representative of such methods." (see page 1940 of MacFerrin et al.), one of ordinary skill in the art would have been motivated to use the ECPCR methodology of MacFerrin et al. to produce the U6 promoter-based siRNA expression cassette of Lois-Caballe et al. In addition, Lois-Caballe et al. also suggested that one can utilize any art-recognized methodology including PCR so as to produce the U6 promoter-containing siRNA expression cassette, wherein each strand of the double-stranded siRNA sequence is operably linked to the U6 promoter and the termination sequence, thereby forming a structure wherein the sense strand (or the antisense strand) is flanked by the U6 promoter and the termination sequence. Further, since the target-specific siRNA sequence is the variable that is "added" into an expression cassette as "new sequence information" when making expression cassettes encoding different siRNA sequences, it would have been obvious to one of ordinary skill in the art to make a pair of PCR primers that hybridize with the constant nucleotide sequence, which is the human U6 promoter sequence recognized in the art to be suitable for transcribing siRNA sequences as taught by Lois-Caballe et al., whether or not one were to construct a cassette that synthesizes only one strand or both strands of a double-stranded siRNA sequence. Note the claim language ambiguity as noted in the 112, second paragraph rejections hereinabove. Since all skills, knowledge, and information necessary to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time the invention was made, in particular those pertaining to designing and making suitable PCR primers that can effectively amplify a desired expression construct (e.g., "PCR permits targeted amplification of DNA sequences."; "The specific segment of DNA amplified in PCR is dictated by the choice of base-pairing sites for oligonucleotide primers."; "DNA sequences of the primers

are incorporated entirely into the product DNA"; see page 1937 of MacFerrin et al. See also column 18, lines 5-9 of Lindermann et al., which teach that "It is within the skill of the art to prepare either type of [phosphorylated or non-phosphorylated] primer by automated synthesis."; see column 5 of Livache et al., which teaches that PCR is "well known" and see column 6 that teaches that one can use PCR primers containing promoter sequences), the claims taken as a whole would have been prima facie obvious at the time of filing.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Primary Examiner
Art Unit 1635

/Dana Shin/
Primary Examiner, Art Unit 1635